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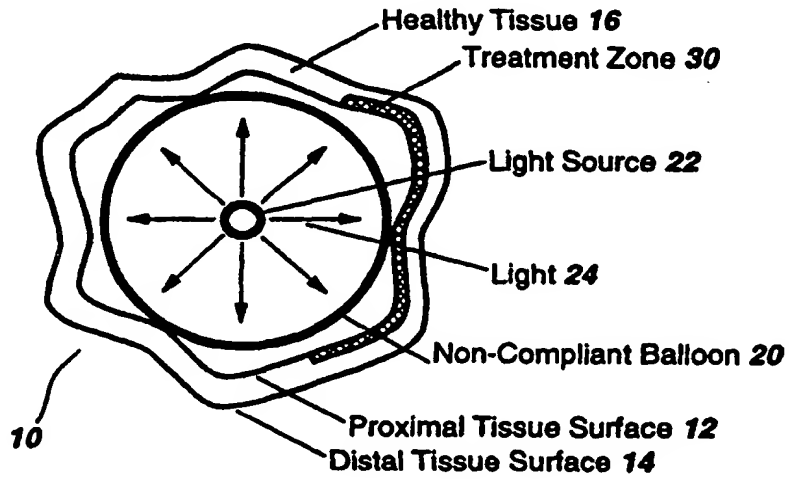
(54) Title: IMPROVED METHOD FOR TARGETED TOPICAL TREATMENT OF DISEASE

(57) Abstract

A method and apparatus for topical treatment of diseased tissue, including topical or systemic application of a PDT agent to diseased tissue, followed by topical application of light (24).



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Improved Method For Targeted Topical Treatment Of Disease

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of USSN 08/739,801, filed October 30, 1996.

The present invention is related to a method and apparatus for topical treatment of tissue, particularly diseased tissue, using photodynamic therapy (PDT) and a PDT agent. More specifically, the present invention is directed to a method and apparatus for topical or systemic application of the PDT agent to the diseased tissue and then topical application of light to the diseased tissue.

PDT was developed to treat cancer and other diseases with the promise of limiting the invasiveness of the therapeutic intervention and lessening potential collateral damage to normal, non-diseased tissue. Key elements of PDT include either selective application or selective uptake of a photosensitive agent into the diseased tissue and site-directable application of an activating light. PDT agents are typically applied systemically (for example, via intravenous injection or oral administration) or via localized topical application directly to diseased tissues (for example, via topical creams, ointments, or sprays). Subsequent to administration of the agent (typically 30 minutes to 72 hours later), an activating light is applied to the disease site, locally activating the agent, and destroying the diseased tissue. Light is typically applied by direct illumination of the site, or by delivery of light energy to internal locations using a fiberoptic catheter or similar means.

Most current PDT regimens are based on systemic application of porphyrin-based agents or topical or systemic application of psoralen-based agents. Examples of porphyrin-based agents include porfimer sodium (PHOTOFRIN®), hematoporphyrin-derivative (HPD), or $SnET_2$. PHOTOFRIN® is one of the few agents currently licensed by the FDA. Porphyrin-based agents generally are derived from complex mixtures of natural or synthetically prepared materials. Many components of porphyrin-based agents are lipophilic. As a result of this lipophilicity, porphyrin-based agents have shown a slight tendency to preferentially accumulate in some tumors. However, the targeting of such agents to diseased tissue is still unacceptably low when compared to uptake in normal tissue, (i.e., 2-10x greater uptake in diseased tissue relative to normal tissue).

Further, porphyrin-based agents were developed primarily as a result of a desire to have agents that are compatible with highly-penetrating activating light so as to enable

treatment of deep-seated cancerous tumors. For example, porphyrin-based agents are typically activated using light at wavelengths from 600-750 nm, which may penetrate tissue to a depth of 1 cm or more. In contrast, light at wavelengths below 600 nm will penetrate tissue only to a depth much less than 1 cm.

However, the dark toxicity of most porphyrin-based agents is high. Dark toxicity is the cellular toxicity in the absence of activating light. Only a small increase in cytotoxicity is achieved upon illumination which necessitates high dosages of agent in order to effect treatment in specific tissues. Moreover, the systemic clearance time, which is the duration subsequent to agent administration wherein significant agent concentrations are present in skin and other external tissues, can extend from weeks to months, forcing patients to avoid exposure to bright light or sunlight for extensive periods in order to avoid serious skin irritation and other complications. Systemic administration also necessitates a delay of between 30 min to 72 hours between agent administration and light activation, essentially precluding the possibility of immediate treatment of diseased tissue upon detection of such diseased tissue. Further, detection and treatment of gastrointestinal diseases, such as Barrett's esophagus) requires at least two endoscopic procedures: one procedure to diagnose, and a subsequent procedure to treat the diseased tissue with light following administration of a PDT agent.

The absence of a significant difference between light and dark cytotoxicity and the low preferential concentration ratio of most common PDT agents necessitates use of high agent dosages. For example, the dosage for treatment of an adult male with PHOTOFRIN® may require greater than 100 mg of agent at a cost of more than $5,000 for the agent alone. This large dose also gives rise to a significant potential for development of adverse side effects in healthy tissue (such as skin phototoxicity) that may remain for several weeks. Also, since porphyrin-based agents are activated with light at wavelengths greater than 600 nm (i.e., near infrared light (NIR)), procedures based on porphyrins + NIR can subject the patient to significant risk of serious complications due to the tissue penetration potential of such NIR light. Complications can include perforation of internal structures, such as the esophagus during treatment of esophageal disease, due to undesirable activation of the agent present in healthy tissue layers which are beyond the topical treatment site.

Additionally, porphyrin-based PDT agents achieve light-activated cytotoxicity via type-II mechanisms, typically the conversion of cellular O_2 into cytotoxic singlet oxygen.

Because cellular O_2 levels can be readily depleted during activation of a type-II PDT agent, use of such agents mandates relatively low intensity illumination and thus relatively long illumination durations in order to allow O_2 levels to remain sufficient throughout the duration of light activation. For example, in the treatment of Barrett's esophagus with PHOTOFRIN®, light intensities typically must be held well below 100-150 mW/cm^2 during treatment, necessitating illumination periods of 10-20 minutes or more. Numerous practitioners have also found with type-II agents that it is equally important to avoid any tissue manipulation that might compromise blood circulation at the treatment site during illumination, again in order to avoid potential depletion of available O_2. Thus, careful control of the illumination apparatus and procedure is critical in order to assure that proper light intensities are delivered without affecting tissue in a manner that might affect blood circulation.

Barrett's esophagus is a perfect example of a superficial disease that is an attractive candidate for PDT as it occurs in a location that is difficult to access via conventional surgical means but is readily accessible using endoscopic catheters. It is a condition in which chronic acid reflux from the stomach irritates the esophagus at the gastro-esophageal junction, causing epithelial tissue in the esophagus to proliferate. Patients with Barrett's esophagus have a significantly increased risk of developing esophageal cancer. The FDA has approved PDT (PHOTOFRIN® with light at 630 nm) to destroy the proliferating tissue in Barrett's patients. Similar regimens can also be used to remove esophageal stricture caused by esophageal cancer.

A common method for treatment of Barrett's esophagus using PDT is shown in cross-sectional form in Fig. 1(a). The esophagus 10 has a proximal tissue surface 12 and a distal tissue surface 14. In the example shown in Fig. 1(a), a portion of esophagus 10 is healthy tissue 16 while another portion is diseased tissue 18. Typically, a non-compliant balloon 20 inserted into the esophagus 10 is used to stabilize the tissue to be treated. The balloon is filled with gas or liquid so that it will expand to a known radius (nearly filling the esophagus) while avoiding dilation of the esophagus. Such dilation could cause restriction of blood flow to the treatment site which could compromise the O_2 supply during light activation. An optical fiber inserted into the center of the balloon 20 serves as a light source 22 to provide a uniform light intensity at the surface of the balloon. The outer structure of this balloon 20 may be composed of a material that scatters activating light 24 or may be transparent to the activating light.

PDT agent present in tissue located proximal to the balloon (on the proximal tissue surface 12) is thereby activated by light emitted from the surface of the balloon 20. Because the balloon 20 is non-compliant, it is possible to estimate the light intensity at the surface of the balloon based on geometrical properties of the balloon and knowledge of the light emitting properties of the light source 22. A fiberoptic diffuser tip is an example of such a light source. However, since the external surface of the balloon 20 generally will not conform exactly to the shape of the esophagus, it is not possible to accurately estimate light intensity at all points along the circumference of the proximal tissue surface 12. Moreover, should the light field present at the proximal tissue surface 12 be uneven, for example due to non-uniform light emitting properties of the light source 22 or incorrect location of the light source 22 in the esophagus 10, uneven treatment may result. In extreme cases, such uneven treatment can compromise tissue sufficiently to result in tissue perforation and patient death.

As shown in Fig. 1(b), activation of the PDT agent in the esophageal tissue upon illumination will produce a treatment zone 26 which will generally include the entire zone of diseased tissue 18 in Fig. 1(a) and may extend radially and circumferentially a significant distance beyond the margins of the zone of diseased tissue 18. In fact, use of NIR light for agent activation can result in formation of a treatment zone that extends a significant distance from the proximal tissue surface 12 to the distal tissue surface 14 of the esophagus 10. This is a consequence of the large penetration depths characteristic of NIR light and the presence of a significant systemic concentration of agent in healthy tissue. In extreme cases, this enlargement of the treatment zone can compromise healthy tissue sufficiently enough to result in tissue perforation and patient death.

This example of the use of PDT for treatment of superficial lesions illustrates a number of disadvantages of current methods and apparatus. For example:

(1) Systemic agent application is costly due to high agent dosage requirements;

(2) Systemic agent application results in sensitization of healthy tissue outside of the desired treatment zone;

(3) Systemic agent application results in prolonged skin photosensitization;

(4) Systemic agent application requires significant delay between disease diagnosis and disease treatment in order for the agent to reach the diseased tissue while clearing out of the surrounding healthy tissue;

(5) Systemic agent application provides PDT practitioners with limited control over the site of agent delivery and concentration;

(6) Systemic agent application results in uneven treatment due to uneven partitioning of the agent into the diseased tissues;

(7) Use of type-II agents requires slow and lengthy agent activation to avoid O_2 depletion;

(8) Use of type-II agents requires careful tissue handling to avoid restriction of blood flow and the resultant O_2 depletion during tissue illumination; and

(9) Use of type-II agents, when commonly combined with NIR activating light, results in excessive treatment depths in most topical applications, adversely affecting surrounding healthy tissue.

Therefore, it is an object of the present invention to provide new methods and apparatus for an improved application of PDT while increasing the efficacy and safety of the procedure and reducing the cost of treatment.

SUMMARY OF THE PRESENT INVENTION

The present invention is directed to a method and apparatus for topical treatment of diseased tissue, including topical or systemic application of a PDT agent to diseased tissue, followed by topical application of light. In general, the method involves the steps of applying a PDT agent to diseased tissue to form a treatment zone; purging excess agent; and applying light to the treatment zone to activate agent associated with the diseased tissue. The light penetrates the treatment zone while minimizing activation of the agent outside the treatment zone.

In a preferred embodiment, Rose Bengal is the PDT agent.

In a further embodiment, the PDT agent is directly applied only to the treatment zone. Alternatively, the PDT agent can be applied systemically.

In a still further embodiment, the depth of activation of the PDT agent is controlled by proper selection of wavelength of activating light so as to avoid activation of agent that may be present in underlying healthy tissues.

In yet a further embodiment, the diseased tissue is diagnosed before applying the PDT agent.

In another embodiment, detection and treatment of a lesion may be effected in a short time period using a single procedure (such as endoscopy) instead of by separate diagnostic and therapeutic procedures.

In another embodiment, treatment rate is not limited by oxygen-dependent mechanisms.

In another embodiment, heat is also applied to the treatment zone to increase efficacy of activation of the agent.

In still another embodiment, activating light is delivered through a "balloon" or other delivery apparatus located at the disease site.

In another embodiment, the method of the present invention can be used for treatment of disease in the gastrointestinal tract.

The method of the present invention can also be used for treatment of disease in vessels of the circulatory system.

The present invention is also directed to an apparatus for topical treatment of diseased tissue.

Accordingly, the present invention is directed to a method and apparatus to improve the evenness of light delivery, and to improve the safety and efficacy and reduce the cost of PDT, for treatment of Barrett's esophagus and other conditions.

BRIEF DESCRIPTION OF THE DRAWINGS

In describing the preferred embodiments, reference is made to the accompanying drawings wherein:

FIGURE 1(a) shows a cross-sectional view of an esophagus illustrating a common method for treatment of Barrett's esophagus using PDT;

FIGURE 1(b) illustrates the treatment zone of the method of Figure 1(a);

FIGURE 2(a) illustrates an example of an embodiment of the present invention for treatment of diseased esophageal tissue;

FIGURE 2(b) illustrates an alternate example of the embodiment of Figure 2(a);

FIGURE 2(c) illustrates an additional alternate example of the embodiment of Figure 2(a);

FIGURE 3(a) illustrates an example of another embodiment for the treatment of disease in vessels of the circulatory system; and

FIGURE 3(b) illustrates an alternate example of the embodiment of Figure 3(a) wherein the PDT agent is directly applied to the diseased tissue.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

The method and apparatus of the present invention is applicable to improved treatment of various dermatologic afflictions, such as psoriasis or skin cancer, and to diseased tissues at sites within the body, such as disease of the digestive or respiratory tracts. The present invention can also be used for the treatment of other anatomical sites, including intra-abdominal, intra-thoracic, intra-cardial, intra-circulatory, intra-cranial, and the reproductive tract.

In general, the method of the present invention involves one or more of the following steps. Initially, disease is diagnosed using, for example, histologic examination, or by measurement of the autofluorescence properties of diseased tissue or by detecting selective uptake of an indicator agent, such as a fluorescent dye or a PDT agent, into such diseased tissue. Thereafter, a sufficient quantity of a topical or systemic formulation of a desired PDT agent is applied to the disease site so as to cover, perfuse, or saturate the diseased tissue. After a brief accumulation period to allow the agent to coat, perfuse, or otherwise become active within the diseased tissue, excess agent is purged or flushed from the disease site, and a substantially uniform light field is applied to the disease site in order to activate the agent associated with the diseased tissue.

For treatment of superficial diseased tissue, the wavelength of the light is preferably chosen so as to allow optical penetration into the diseased tissue but to minimize further optical penetration beyond the diseased tissue into underlying healthy tissue. For example, visible light in the spectral region between 400-600 nm may be used to afford shallow penetration depths on the order of several millimeters or less. Use of such light affords efficacy in agent activation in superficial diseased tissues while simultaneously minimizing potential for deleterious photosensitization of underlying tissue. Preferably, laser light is used. It can be delivered by fiberoptic catheters. Alternatively, light can be delivered by direct illumination. Other alternate light source configurations and delivery apparatus include fiberoptic bundles, hollow-core optical waveguides, and liquid-filled waveguides. Alternate light sources, including light emitting diodes, micro-lasers, monochromatic or continuum lasers or lamps for production of activating light, and continuous wave or pulsed lasers or lamps. Either single-photon or two-photon excitation methods can be used for agent activation. A more detailed explanation of such excitation methods is given

in commonly assigned application serial no. 08/739,801 filed October 30, 1996 which is incorporated herein by reference.

Furthermore, the time and order of the applications of the agent and light can also be varied. For example, application of the agent and the light treatment regimen can be repeated one or more times to eliminate residual diseased tissue. Further, for some applications, an increased delay between agent application and light treatment can be beneficial. Additionally, the step of diagnosing can almost immediately be followed by the steps of applying a PDT agent, purging excess agent and applying light so that said method of diagnosis and treatment is done in a single procedure. If PDT agent uptake is used to diagnose or detect diseased tissue, the step of diagnosing can be immediately followed by the step of applying activating light. Alternatively, there may be an indefinite delay between diagnosis and PDT treatment.

Preferably Rose Bengal is used as the PDT or photosensitizing agent as it is inexpensive, non-toxic, has a proven safety record in human use, has significant intrinsic lipophilic properties, exhibits both type-I and type-II PDT response and therefore can be activated by type-I, oxygen-independent mechanism and is strongly phototoxic upon activation with light between 500 nm and 600 nm. Because of its O_2-independent response, Rose Bengal is compatible with high intensity light activation, which reduces treatment time relative to porphyrin-based agents. More specifically, Rose Bengal is optimally activated using light between 500 nm and 600 nm, which is sufficient for activation of superficial diseased tissue and substantially avoids the potential for activation of underlying healthy tissues. An example of such a PDT agent is a solution of Rose Bengal formulated with a suitable lipophilic delivery vehicle, such as 1-octanol or liposomes.

Alternatively, other PDT agents, including type-I or type-II agents can be used. Examples of such standard PDT agents include psoralen derivatives; porphyrin and hematoporphyrin derivatives; chlorin derivatives; phthalocyanine derivatives; rhodamine derivatives; coumarin derivatives; benzophenoxazine derivatives; chlorpromazine and chlorpromazine derivatives; chlorophyll and bacteriochlorophyll derivatives; pheophorbide a (Pheo a); merocyanine 540 (MC 540); Vitamin D; 5-amino-laevulinic acid (ALA); photosan; pheophorbide-a (Ph-a); phenoxazine Nile blue derivatives including various phenoxazine dyes; PHOTOFRIN; benzoporphyrin derivative mono-acid; $SnET_2$; and

Lutex. The inventors of the present invention believe that all present and future PDT agents will work in the method and apparatus of the present invention.

Additionally, the present invention is not limited to the use of one PDT agent. Instead, more than one PDT agent can be used during a treatment regimen.

In a further embodiment, the PDT agent used in the present invention can include at least one targeting moiety. Examples of such targeting moieties include DNA, RNA, amino acids, proteins, antibodies, ligands, haptens, carbohydrate receptors or complexing agents, lipid receptors or complexing agents, protein receptors or complexing agents, chelators, and encapsulating vehicles. Such targeting moieties may be used to improve the selectivity of agent delivery to diseased tissue, and can function either by association with the photosensitizing PDT agent (for example where the PDT agent is encapsulated in a vehicle composed of the targeting moiety) or by attachment to the photosensitizing PDT agent (for example where the PDT agent is covalently attached to the targeting moiety).

In a further preferred embodiment, the PDT agent is applied directly to the diseased tissue. Employment of direct topical application provides a number of advantages. In particular, it affords improved targeting of the agent specifically to the diseased tissue, reduces the required latency period between agent administration and light activation and thereby shortens the treatment cycle, substantially eliminates the potential for systemic photosensitization, reduces agent consumption, and reduces the overall potential for side effects from exposure to the agent. Preferably, the agent is applied as a topical spray or wash. After a brief accumulation period (generally not to exceed 30 minutes), the excess agent is removed from the tissue surface by flushing with liquid, such as with water or saline. Following this flushing, it is preferred that the residual agent associated with the diseased tissue be activated by illumination of the diseased site with visible light between 400 nm and 600 nm. Optically, the light can be applied as discussed supra.

Alternatively, the PDT agent can be applied systemically. For example, this application may be via intravenous injection or parenteral administration (such as by consumption of a tablet or liquid formulation of the PDT agent).

In a further embodiment, heat can be applied to the treatment zone to increase PDT effectiveness via hyperthermia. Heat can be applied, for example, through the use of a heated liquid in an illumination balloon, a transparent heating pad positioned between the

illumination source and the tissue, or simultaneous illumination of the treatment site with infrared energy.

Examples of some of these embodiments of the present application are shown in cross-sectional form in Figs. 2(a), 2(b), and 2(c).

Fig. 2(a) illustrates an example of a treatment of diseased esophageal tissue using a non-compliant balloon 20 illumination apparatus. Initially, a treatment zone 30 is identified. This can be done for example via endoscopic examination of the esophagus and visual or spectroscopic identification of zones of diseased tissue. Such identification can include detection of histologic changes or other visual indicators of disease, detection of changes in autofluorescence, or detection of uptake of PDT or other agents into diseased tissue. Following identification of the treatment zone 30, PDT agent is applied to the identified diseased tissue. This agent can be applied, for example, via systemic application or more preferably, by direct spray application using a nozzle or other means provided at the distal end of an endoscope. Excess agent is subsequently purged from the site by, for example, natural systemic clearance or by flushing with liquid.

A transparent, non-compliant balloon apparatus 20 is then inserted into the esophagus so as to span the treatment zone 30. The non-compliant balloon 20 is filled with gas or liquid to a pre-determined pressure so as to establish a desired pre-determined radius. Visible light 24 is then uniformly delivered radially to the treatment site through the walls of the balloon 20 using a light source 22, such as for example a fiberoptic diffuser, located along the central axis of the balloon.

Additionally, the balloon 20 can be filled with a scattering medium, such as a dilute solution of intralipid, so as to improve the uniformity of light intensity delivered at the surface of the balloon. Further, the balloon 20 can be composed of or include a material that scatters the light 24 delivered at the surface of the balloon so as to further improve the uniformity of light intensity delivered at the surface of the balloon. Examples of such a material include a material that is naturally translucent, such as latex; a polymer that includes particulate scattering materials; or a polymer with a roughened surface.

In the example illustrated in Fig. 2(a), the intensity of the light source 22 is operated at a pre-determined level for a pre-determined duration based on the filled radius of the non-compliant balloon 20 and the desired light intensity and light dose at the surface of the balloon.

An alternate example of this embodiment is shown in cross-sectional form in Fig. 2(b), where diseased esophageal tissue is treated using an enlarged non-compliant balloon 40. In this example, following identification of diseased tissue, PDT agent is applied to the identified diseased tissue. Excess agent is subsequently purged from the site.

A transparent, non-compliant balloon apparatus 40 is then inserted into the esophagus so as to span the treatment zone 30. The non-compliant balloon 40 is filled with gas or liquid so as to substantially distend or slightly dilate the esophagus, eliminating folding of the esophageal surface and thereby presenting a more uniform tissue surface 12 for illumination. Fill pressure is measured to establish the radius of the filled balloon. Visible light 24 is then uniformly delivered radially to the treatment site through the walls of the balloon using a light source 22, such as for example a fiberoptic diffuser, located along the central axis of the balloon.

Additionally, the balloon 40 can be filled with a scattering medium, such as a dilute solution of intralipid, so as to improve the uniformity of light intensity delivered at the surface of the balloon. Further, the balloon 40 can be composed of or include a material that scatters the light 24 delivered at the surface of the balloon. Examples of such materials include material that is naturally translucent, such as latex; a polymer that includes particulate scattering materials; or a polymer with a roughened surface.

The pressure used to fill the balloon is measured and used to establish the operational radius of the filled balloon, and the intensity of the light source 22 is operated at a level that is selected based on the operational radius of the filled non-compliant balloon 40 so as to deliver a desired light intensity and light dose at the surface of the balloon. It is preferred in this alternate embodiment that sufficient pressure be used so as to minimize folding of the treated esophageal region without significantly dilating the esophagus so as to avoid potential stenosis or other non-specific irritation of esophageal tissue.

An additional alternate example of this embodiment is shown in cross-sectional form in Fig. 2(c), where diseased esophageal tissue is treated using a compliant balloon 50. In this example, following identification of diseased tissue, PDT agent is applied to the identified diseased tissue. Excess agent is subsequently purged from the site.

A transparent, compliant balloon apparatus 50 is then inserted into the esophagus so as to span the treatment zone 30. The compliant balloon 50 is filled with gas or liquid so as to fill, distend or slightly dilate the esophagus, substantially eliminating non-uniform

contact between the esophageal surface and the balloon and thereby presenting a uniform tissue surface for illumination. Fill pressure is measured to establish the approximate radius of the filled balloon. Visible light 24 is then uniformly delivered radially to the treatment site through the walls of the balloon 50 using a light source 22, such as for example a fiberoptic diffuser, located along the central axis of the balloon.

Additionally, the balloon 50 can be filled with a scattering medium, such as a dilute solution of intralipid, so as to improve uniformity of light intensity delivered at the surface of the balloon. Further, the balloon 50 can be composed of or include a material that scatters the light 24 delivered at the surface of the balloon. Examples of such materials include material that is naturally translucent, such as latex; a polymer that includes particulate scattering materials; or a polymer with a roughened surface.

The pressure used to fill the balloon is measured to establish the operational radius of the filled balloon. Thus, in this example, the intensity of the light source 22 is operated at a level that is selected based on the operational radius of the filled compliant balloon 50 so as to deliver a desired light intensity and light dose at the surface of the balloon. Preferably, in this alternate embodiment, sufficient pressure is used so as to minimize folding of the treated esophageal region without significantly dilating the esophagus (to avoid potential stenosis or other non-specific irritation of esophageal tissue).

For the treatment of disease in vessels of the circulatory system (such as arterial or venous plaque), Figs. 3(a) and 3(b) illustrate an alternate preferred embodiment of the present invention

In the specific example of Fig. 3(a), a photosensitive agent is applied parenterally or via intravenous injection. The agent accumulates in diseased tissue of the vessel wall 60 to form a treatment zone 62. This agent is chosen based on preferential concentration in diseased material present at the desired treatment zone. After a brief accumulation period, a light 64 is applied to the disease site in order to activate the agent associated with the diseased material. This application may be effected by using a fiberoptic catheter 66 or similar means having a focusing, collimating, or diffusing terminus for spatial control of light delivery. The fiberoptic catheter 66 is able to deliver the light 64 directly to the treatment zone 62 so that the light can be applied topically. To minimize potential optical penetration into underlying healthy tissue, it is preferred that visible light in the spectral region between 400-600 nm be used so as to effect shallow penetration depths on the order of several millimeters or less. Use of such light affords efficacy in agent activation

in superficial diseased material while simultaneously minimizing potential for deleterious photosensitization of the underlying tissue.

Alternatively, the photosensitive agent administration can be effected via localized, direct application of an agent to diseased material in the treatment zone 62, as illustrated in Fig. 3(b). Agent administration may be readily effected via an agent delivery device 68, such as a capillary tube, attached to and terminating near the end of the fiberoptic catheter 66, that is used to deliver a small quantity of agent, as a stream 70 or other flow, directly to or in the vicinity of the treatment zone 62. Alternately, this delivery device 68 may be separate from the fiberoptic catheter 66, thereby facilitating independent position of the respective termini of the light delivery fiberoptic catheter 66 and the agent delivery device 68. In either embodiment, delivery of a small quantity of photosensitive agent to diseased material in the treatment zone 62 is followed, after a short accumulation period, with application of light 64 to the disease site in order to activate agent associated with diseased material.

Preferably, in these example embodiments, Rose Bengal is used as the photosensitizing agent. Rose Bengal is optimally activated using light between 500 nm and 600 nm, which is sufficient for activation of superficial diseased material and substantially avoids potential for activation of underlying healthy tissues. Further, this agent is compatible with high intensity activating light, which may thereby be used to substantially reduce treatment times over that required with other agents, such as Type-II PDT agents.

This description has been offered for illustrative purposes only and is not intended to limit the invention of this application, which is defined in the claims below.

What is claimed as new and desired to be protected by Letters Patent is set forth in the appended claims.

CLAIMS:

1. A method for topical treatment of diseased tissue, said method comprising the steps of:

applying a PDT agent to said diseased tissue to form a treatment zone;

purging excess agent; and

applying light to said treatment zone to activate agent associated with said tissue, wherein said light penetrates said treatment zone while minimizing activation of said agent outside said treatment zone.

2. The method of Claim 1 wherein said light is at a wavelength so that said light penetrates said treatment zone while minimizing further penetration into surrounding tissue.

3. The method of Claim 2 wherein said wavelength is between approximately 400-600 nm.

4. The method of Claim 1 wherein said light activates said agent by single-photon excitation.

5. The method of Claim 1 wherein said light activates said agent by two-photon excitation.

6. The method of Claim 1 wherein said steps of applying a PDT agents, purging excess agent and applying light are repeated one or more times.

7. The method of Claim 1 further comprising the step of diagnosing said diseased tissue before applying said PDT agent.

8. The method of Claim 7 wherein said step of diagnosing includes using autofluorescence properties of said diseased tissue.

9. The method of Claim 7 wherein said step of diagnosing includes detecting selective uptake of an indicator agent.

10. The method of Claim 9 wherein said indicator agent is selected from the group comprising a fluorescent dye and a PDT agent.

11. The method of Claim 7 wherein said step of diagnosing is almost immediately followed by said steps of applying a PDT agent, purging excess agent and applying light so that said method of diagnosis and treatment is done in a single procedure.

12. The method of Claim 7 wherein there is a delay between said step of diagnosing and said step of applying a PDT agent.

13. The method of Claim 1 wherein said PDT agent is Rose Bengal.

14. The method of Claim 13 wherein said light is at a wavelength of between approximately 500-600 nm.

15. The method of Claim 1 wherein more than one PDT agent is applied to said diseased tissue.

16. The method of Claim 1 wherein said PDT agent includes a targeting moiety.

17. The method of Claim 16 wherein said targeting moiety is selected from the group comprising DNA, RNA, amino acids, proteins, antibodies, ligands, haptens, carbohydrate receptors or complexing agents, lipid receptors or complexing agents, protein receptors or complexing agents, chelators, and encapsulating vehicles.

18. The method of Claim 1 wherein said PDT agent is applied directly to said diseased tissue.

19. The method of Claim 1 wherein said PDT agent is applied systemically.

20. The method of Claim 1 wherein said excess agent is purged by natural systemic clearance.

21. The method of Claim 1 wherein said excess agent is purged by flushing said tissue with liquid.

22. The method of Claim 1 further comprising the step of applying heat to said treatment zone to increase the activation of said agent.

23. The method of Claim 1 wherein said light is applied via a balloon catheter apparatus.

24. The method of Claim 23 wherein said balloon catheter apparatus is non-compliant.

25. The method of Claim 24 wherein said non-compliant balloon catheter apparatus is enlarged so as to substantially distend said treatment zone.

26. The method of Claim 23 wherein said balloon catheter is compliant.

27. The method of Claim 23 wherein said balloon catheter is filled with a scattering medium.

28. The method of Claim 23 wherein said balloon catheter comprises a material that scatters light.

29. The method of Claim 1 wherein said light is applied by direct illumination.

30. The method of Claim 1 wherein said light is applied by a light source selected from the group comprising fiberoptic bundles, hollow-core optical waveguides, liquid-filled waveguides, light emitting diodes, micro-lasers, monochromatic lasers, continuum lasers, lamps, continuous wave lasers, and pulsed lasers.

31. A method for treatment of disease in vessels of the circulatory system, said method comprising the steps of:

applying a PDT agent to diseased tissue in said vessel to form a treatment zone; and

applying light to said treatment zone to activate agent associated with said tissue, wherein said light penetrates said treatment zone while minimizing activation of said agent outside said treatment zone.

32. The method of Claim 31 wherein said PDT agent is applied parenterally.

33. The method of Claim 31 wherein said PDT agent is applied via intravenous injection.

34. The method of Claim 31 wherein said light is applied by a fiberoptic catheter.

35. The method of Claim 31 wherein said light is at a wavelength is between approximately 400-600 nm.

36. The method of Claim 31 wherein said PDT agent is applied directly to the diseased tissue.

37. The method of Claim 36 wherein said agent is applied through a capillary tube.

38. The method of Claim 31 wherein said PDT agent is Rose Bengal.

39. The method of Claim 38 wherein said light is at a wavelength of between approximately 500-600 nm.

40. Apparatus for topical treatment of diseased tissue comprising:

a PDT agent for application to said diseased tissue so as to form a treatment zone;

means for purging excess agent; and

a source of light to activate said PDT agent in said treatment zone, wherein said light is able to penetrate said diseased tissue while minimizing activation of said agent outside said diseased tissue.

41. The apparatus of Claim 40 wherein said light is at a wavelength so that said light penetrates said treatment zone while minimizing further penetration into surrounding tissue.

42. The apparatus of Claim 41 wherein said wavelength is between approximately 400-600 nm.

43. The apparatus of Claim 40 wherein said light activates said agent by single-photon excitation.

44. The apparatus of Claim 40 wherein said light activates said agent by two-photon excitation.

45. The apparatus of Claim 40 further comprising an indicator agent to diagnose said diseased tissue by detecting selective uptake of said indicator agent.

46. The apparatus of Claim 45 wherein said indicator agent is selected from the group comprising a fluorescent dye and a PDT agent.

47. The apparatus of Claim 40 wherein said PDT agent is Rose Bengal.

48. The apparatus of Claim 47 wherein said light is at a wavelength of between approximately 500-600 nm.

49. The apparatus of Claim 40 further comprising more than one PDT agent applied to said diseased tissue.

50. The apparatus of Claim 40 wherein said PDT agent includes a targeting moiety.

51. The apparatus of Claim 50 wherein said targeting moiety is selected from the group comprising DNA, RNA, amino acids, proteins, antibodies, ligands, haptens,

carbohydrate receptors or complexing agents, lipid receptors or complexing agents, protein receptors or complexing agents, chelators, and encapsulating vehicles.

52. The apparatus of Claim 40 wherein said PDT agent is applied directly to said diseased tissue.

53. The apparatus of Claim 40 wherein said PDT agent is applied systemically.

54. The apparatus of Claim 40 further comprising heat applied to said treatment zone to increase the activation of said agent.

55. The apparatus of Claim 54 wherein said heat is applied by heated liquid in a balloon catheter apparatus.

56. The apparatus of Claim 54 wherein said heat is applied by a transparent heating pad.

57. The apparatus of Claim 40 wherein said light is applied via a balloon catheter apparatus.

58. The apparatus of Claim 57 wherein said balloon catheter apparatus is non-compliant.

59. The apparatus of Claim 58 wherein said non-compliant balloon catheter apparatus is enlarged so as to substantially distend said treatment zone.

60. The apparatus of Claim 57 wherein said balloon catheter is compliant.

61. The apparatus of Claim 57 wherein said balloon catheter is filled with a scattering medium.

62. The apparatus of Claim 57 wherein said balloon catheter comprises a material that scatters light.

63. The apparatus of Claim 40 wherein said light is applied by direct illumination.

64. The apparatus of Claim 40 wherein said light is applied by a light source selected from the group comprising fiberoptic bundles, hollow-core optical waveguides, liquid-filled waveguides, light emitting diodes, micro-lasers, monochromatic lasers, continuum lasers, lamps, continuous wave lasers, and pulsed lasers.

65. The method of Claim 1 wherein said PDT agent is at least one standard PDT agent.

66. The method of Claim 31 wherein said PDT agent is at least one standard PDT agent.

67. The apparatus of Claim 40 wherein said PDT agent is at least one standard PDT agent.

Fig. 1(a)

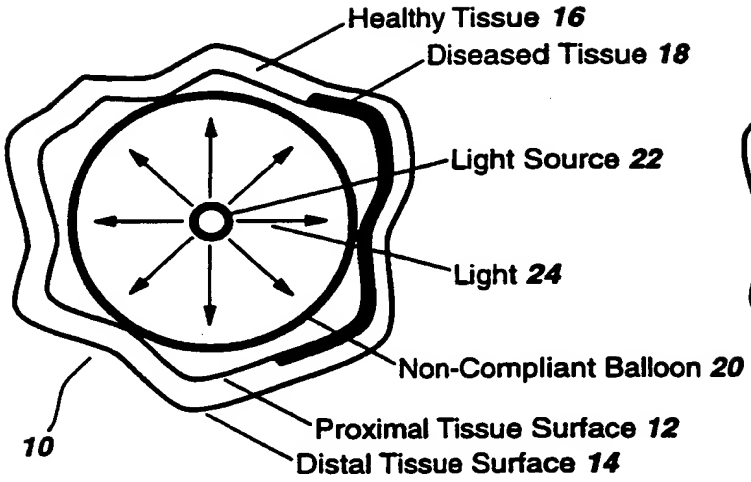


Fig. 1(b)

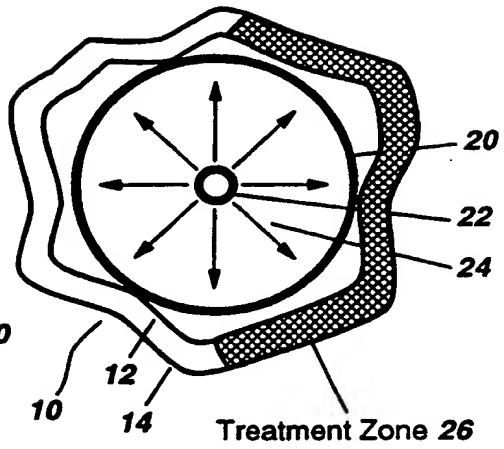


Fig. 2(a)

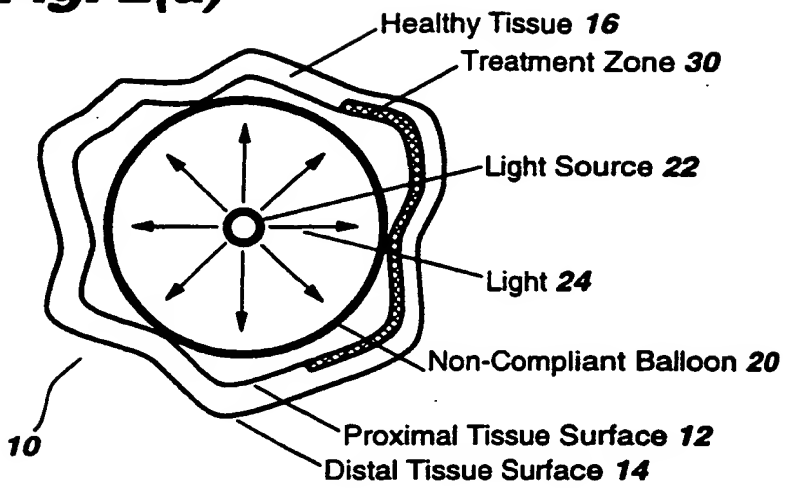


Fig. 2(b)

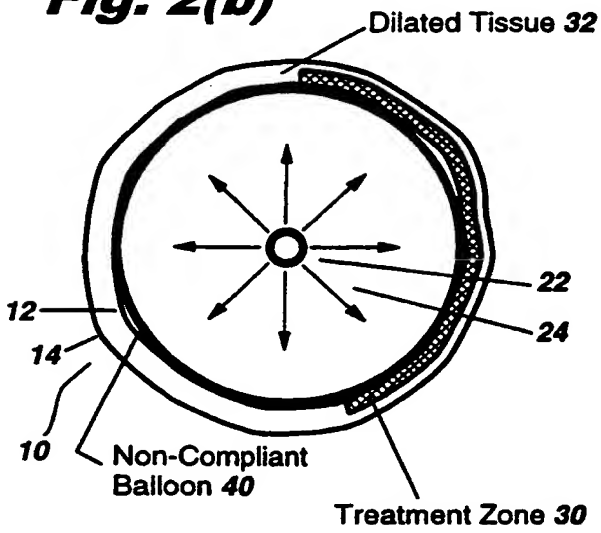


Fig. 2(c)

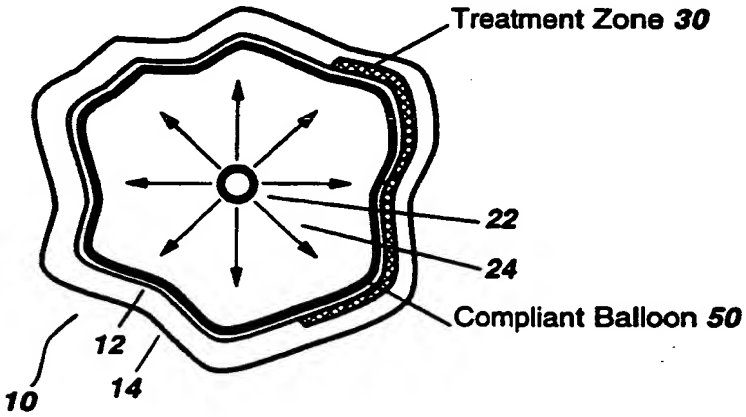


Fig. 3(a)

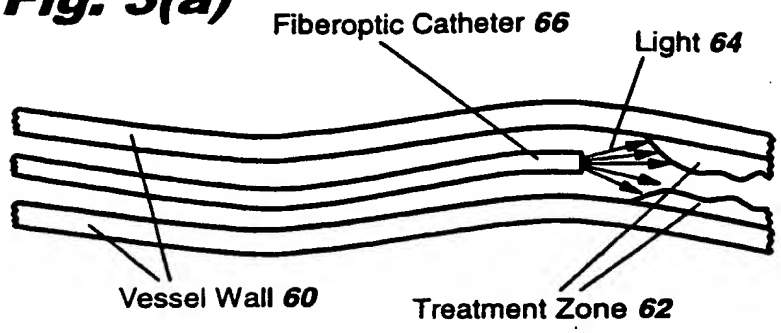
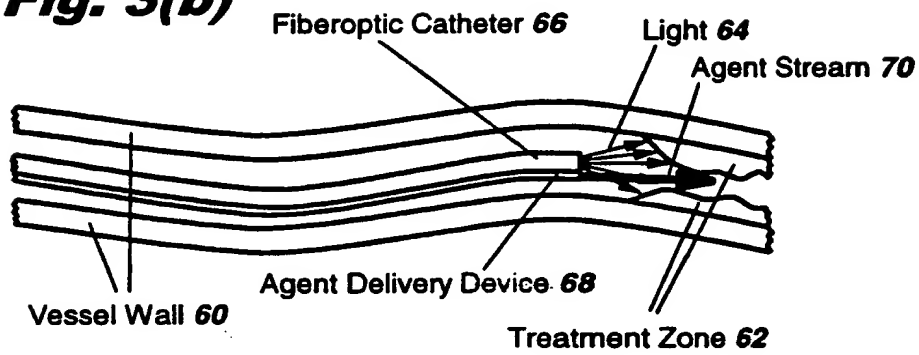

Fiberoptic Catheter 66
Light 64
Vessel Wall 60
Treatment Zone 62

Fig. 3(b)


Fiberoptic Catheter 66
Light 64
Agent Stream 70
Agent Delivery Device 68
Vessel Wall 60
Treatment Zone 62

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/07515

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 19/00
US CL :128/898; 606/2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/898; 250/458.1; 604/20; 606/2, 9; 607/2, 3, 89

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, EAST, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,822,335 A (KAWAI et al.) 18 April 1989, entire document.	40-64, 67
A	US 5,034,613 A (DENK et al.) 23 July 1991, entire document.	1-29, 65
A	STABLES et al., Photodynamic therapy, Antitumour Treatment, Cancer Treatment Reviews (1995) 21, pages 311-323.	1-67
A	KATSUMI et al., Photodynamic Therapy witha Diode Laser for Implanted Fibrosarcome in Mice Employing Mono[L-Aspartyl Chlorn E6, Research Note, Photochemistry, 1996, 64(4), pages 671 to 675.	1-39, 65, 66

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 OCTOBER 1999	Date of mailing of the international search report 17 NOV 1999
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